UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/501,643	02/10/2000	Dr. Larry Sklar	UNME-0070-1	4170

28156 7590 06/30/2004

COLEMAN SUDOL SAPONE, P.C.
714 COLORADO AVENUE
BRIDGE PORT, CT 06605-1601

EXAMINER	
GABEL, GAILENE	
ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/501,643	SKLAR ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-27 and 46-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-27 and 46-54* is/are rejected.

7)☒ Claim(s) *52* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/26/04 has been entered.

Amendment Entry

2. Applicant's amendment and response filed 2/26/04 is acknowledged and has been entered. Claims 48-53 have been added. Accordingly, claims 1-7, 9-27, and 46-53 are pending.

Claim Objections

3. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 50, second occurrence, 51, 52, and 53 have been renumbered as claims 51, 52, 53, and 54, respectively.

Thus, claims 1-7, 9-27, and 46-54 are pending and are under examination.

Rejections Withdrawn

Claim Rejections - 35 USC § 112

4. In light of Applicant's argument, the rejection of claims 1-7, 9-13, 27, 46-51, 53, and 54 under 35 U.S.C. 112, first paragraph, enablement rejection is hereby, withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-7, 9-27, and 46-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, preamble, "detention" should be –detection--.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements that are critical to the practice of the instant invention, such omission amounting to a gap between the elements. See MPEP § 2172.01.
In the specification, Applicant provides specific teaching against separation gas (air bubbles) in flow cytometers with the idea that, optimally, the bubbles should be removed from the sample prior to injection and from the tubing. Applicant specifically provides

however, that peristaltic flow rates of -3 ul /second through common tubing (0.02 inch tubing, 10 rpm or higher) have been determined to be compatible with flow cytometric detection. These essential elements, critical to the practice of the invention, are not recited in the rejected claim.

Claim 48 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements that are critical to the practice of the instant invention, such omission amounting to a gap between the elements. See MPEP § 2172.01. In the specification, Applicant provides specific teaching against air bubbles in flow cytometers with the idea that, optimally, the bubbles should be removed from the sample prior to injection and from the tubing. Applicant specifically provides that peristaltic flow rates of -3 ul /second through common tubing (0.02 inch tubing, 10 rpm or higher) have been determined to be compatible with flow cytometric detection. These essential elements, critical to the practice of the invention, are not recited in the rejected claim.

The recitation of "an inner diameter of less than about 0.03 inch" in claim 50 renders the claim indefinite because it fails to ascertain the requisite degree and scope of the invention. Specifically, the inner diameter encompasses 0.000 inch, which would appear to render the inventive tubing dysfunctional.

The recitation of "said inner diameter is greater than 0.01 inch" in claim 51 renders the claim indefinite because it fails to ascertain the requisite degree and scope of the invention. Specifically, the inner diameter encompasses 10 inches or 100 inches, which would appear to render the inventive tubing dysfunctional.

Claim 52 recites non-idiomatic term and is, therefore, confusing in reciting "certain". Perhaps, Applicant intends to recite, "specific".

The recitation of "said given size (of tubing) is less that about 0.03 inch" in claim 53 renders the claim indefinite because it fails to ascertain the requisite degree and scope of the invention. Specifically, the given size of tubing encompasses 0.00001 inch, which does not appear to be Applicant's intent.

Claim 54 recites non-idiomatic term and is, therefore, confusing in reciting "certain". Perhaps, Applicant intends to recite, "specific".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-3, 5, 7, 9-12, 15-19, 26-27, and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Saros et al. (US 4,853,336) in view of Weigl et al. (US 6,159,739).

Saros et al. disclose a single tubing (channel/conduit) continuous flow analyzer system in which a successive plurality of samples (liquid segments) containing biomaterial and test compounds (analysis mixtures) are separated by immiscible segments which permit delayed on-line mixing of the components in the mixtures in the single conduit (see Abstract, column 2, lines 40-55, column 4, lines 8-26 and Figure 4). Saros et al. specifically disclose a flow system comprising an autosampler for moving a plurality of samples, a means for introducing a separation gas (immiscible intervening segment) between each sample, and the tubing for passage of fluid stream therethrough. The walls of the tubing have an expanded diameter sufficient to render the separation gas, non-occluding (see column 3). The autosampler includes a probe which aspirates the samples, test compounds, reagents (buffer fluid), and the separation gas. The autosampler is connected to a bidirectional linear drive means (see column 5, lines 1-10). Saros et al. disclose that the probe is coated with immiscible liquid. The movement or aspiration of the samples is effected by a peristaltic pump which is located downstream of the system tubing (see column 5, lines 14-21 and column 6, lines 52-55). A metering assembly as in Figure 3 including an array of position sensors, are programmed to detect interface between selected separation air segments, i.e. parameter controlled, and the plurality of samples. Biomaterials in the samples are fluorescently tagged so that fluorescent signals associated with their

function upon reaction with test compounds provide detectable events during analysis (see column 11, lines 23-36). In teaching that the probe and tubing in the flow system is coated with immiscible liquid, Saros et al. is, therefore, said to have inherently anticipated a hydrophobic probe or a probe coated with hydrophobic material.

Saros et al. differ from the instant invention in failing to disclose a flow cytometer for hydrodynamically focusing the fluid stream for analysis of particles in the samples as the fluid stream passes through the flow cytometer.

Weigl et al. disclose a device for 3-dimensional alignment of particles in microfabricated flow channels. Weigl et al. specifically disclose a flow module for reproducibly focusing particles into the measurement zone of a flow cytometer, wherein selective analysis of particles in a plurality of samples takes place (see column 3, lines 22-33). According to Weigl et al., optical flow cytometric measurement takes place by arranging particles in a single file, typically by hydrodynamic focusing within a sheath fluid, then interrogating the particles by a light beam propagating orthogonal to the flow axis. Hydrodynamic focusing is a phenomenon that leads to a single file flow of particles as a result of the very small dimensions of the flow channel (see column 1, lines 17-52).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate a flow cytometer for hydrodynamically focusing a fluid flow stream so as to selectively analyze particles in samples as taught by Weigl into the flow analyzer as taught by Saros because Weigl specifically taught application of flow cytometric measurement zones that utilize hydrodynamic focusing in any

microfabricated flow analyzers, such as for example, the flow analyzer as taught by Saros, having a means to move samples and a means to introduce a separation gas. One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate flow cytometric measurement modules as used by Weigl into the flow analyzer as taught by Saros to create a versatile flow cytometric system capable of analyzing various sample particles because Weigl specifically taught widespread application of flow cytometric measurement modules in analyzing microscopic particles for determining physical and chemical properties in the fields of hematology, immunology, genetics, parasitology, oncology, etc.

7. Claims 4, 6, 13-14, 20-24, 46, 47, 49-51, and 53-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saros et al. (US 4,853,336) in view of Weigl et al. (US 6,159,739) as applied to claims 1-3, 5, 7, 9-12, 15-19, 26-27, and 48 above, and further in view of Kercso et a. (US 6,132,685).

Saros et al. and Weigl et al. have been discussed supra. Saros et al. and Weigl et al. differ from the claimed invention in failing to disclose the source well, as a well plate comprising 96, 384, or 1536 source wells. Saros et al. and Weigl et al. further differ in failing to disclose that the flow tubing or channels are made of polyvinyl chloride (PVC).

Kercso et al. disclose high throughput microfluidic flow systems for analyzing a large number of sample compounds. The samples to be analyzed are contained in standard multiwell microtiter plates such as those having 96, 384,1536, or higher

numbers of wells and are transferred sequentially from the wells into a tubing or channel system. These multiwell plates travel along a conveyor system between an input stack and an output stack, and are sequentially aligned in the input port for autosampling by a tubular autosampler (pipettor) which extends below affixed to the microfluidic channel substrate (see column 3 and 11). These microfluidic flow channels are fabricated on the planar substrate comprising polymeric materials which are inherently hydrophobic such as polyvinylchloride (PVC) and polyurethane.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute the sample source taught by Saros as modified by Weigl, with the microtiter plates taught by Kercso because Saros specifically taught sequentially analyzing a successive numbers of samples which are separated by immiscible segments in order to effect analysis of a plurality of samples using the flow cytometer as taught by Weigl and Kercso specifically taught the advantage of using multiwell plate sampling for handling and sequentially introducing even larger numbers of samples to effect analysis thereto. One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the multiwell plates of Kercso into the flow analyzer taught by Saros as modified by Weigl because Kercso specifically taught the added advantage of rapid and expedient analysis of large numbers of samples and test compounds in small volumes achieved by their sequential introduction from multiwell structures into automated flow analyzer and microfluidic systems.

Saros et al., Weigl et al., and Kercso et al. differ in failing to disclose that the flow tubing or channels made of PVC have an inner diameter of 0.01 to 0.03 inches and a wall thickness of 0.01 to 0.03 inches, such as recited in claim 13 or an inner diameter of 0.02 inches and a wall thickness of 0.02 inches, such as recited in claim 14. Further, Saros et al. and Kercso et al. fail to disclose that a portion of the fluid stream passing through the pump is contained within a tube having an internal diameter of 0.02 inches or less, or less than about 0.03 inch, or greater than about 0.01 inch, and a rate of at least six samples per minute, such as recited in claim 46, 47, 50, 51, 53, and 54. Saros et al. and Kercso et al. also fail to disclose that the probe has a conical tip and the source wells on the microwell plates have conical shapes as well.

However, it is maintained that parameter requirements in flow systems or microfluidic channels such as inner diameter of 0.01 to 0.03 inches and wall thickness of 0.01 to 0.03 inches, or volumetric capacity of tube having an internal diameter of 0.02 inches or less ,or shape requirements of autosampling probe tips such as tubular or conical shapes/structures are all result effective variables which the prior art references have shown may be altered in order to achieve optimum results. It has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum parameter of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454, 456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation." Id. at 458, 105

USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272, 276, 205 USPQ 215, 218-219 (C.C.P.A. 1980). Since Applicant has not disclosed that the specific limitations recited in instant claims 13, 14, 4, 24, 46-47, 50, 51, 53, and 54 are for any particular purpose or solve any stated problem and the prior art teaches that flow analysis system requirements often vary according to the samples, types, and numbers thereof, being analyzed and various parameters taught by the prior art appear to work equally as well; absent unexpected results, it would have been obvious for one of ordinary skill to discover the optimum workable parameters and requirements of the methods disclosed by the prior art by normal optimization procedures.

8. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Saros et al. (US 4,853,336) in view of Weigl et al. (US 6,159,739) as applied to claims 1-3, 5, 7, 9-12, 15-19, 26-27, and 48 above, further in view of Kercso et a. (US 6,132,685), and in further view of Farrell et al. (US 5,788,927).

Saros et al., Weigl et al., and Kercso et al. have been discussed supra. Saros et al., Weigl et al., and Kercso et al. differ in failing to teach that the well plate is mounted in an inverted position.

Farrell et al. teach a flow analyzer system which incorporates an automated sample aspiration design into its hydraulic system wherein a sealed sample source is inverted and moved relative to the probe of the autosampler for autosampling. The

probe tip or needle of the autosampler penetrates the seal of the sample source to aspirate the sample contained within (see column 7).

The inverted mounting design of the well plate as recited in claim 25 has been specifically suggested by Farrell et al. for incorporation into flow analyzers such as those taught by Saros, Weigl, and Kercso and constitutes an obvious modification or design choice of autosampling or sample positioning, which is routinely varied in microfluidic or flow cytometric systems and which has not been described as being critical to the practice of the invention.

Response to Arguments

9. Applicant's arguments filed 2/26/04 have been fully considered but they are not persuasive.

A) Applicant argues that the prior art teaches away from the invention defined in claim 1. Applicant contends that prior art clearly holds that separation gas is not to be introduced into a fluid flow stream that is being fed to a flow cytometer that hydrodynamically focuses the fluid flow stream. Applicant thus argues that one of ordinary skill in the art would be motivated against combining the teachings of Saros et al. with the teachings of Weigl et al.

In response, use of "comprising" language in congruent to the recited claim, does not exclude the teaching of Saros in combination with the flow cytometer of Weigl. Specifically, claim 1 recites:

A flow cytometry apparatus ... comprising,

means for moving ... samples ... into a flow stream,

means for introducing separation gas between ... samples in said flow stream,

a flow cytometer for hydrodynamically focusing ... and selectively analyzing particles in each of said plurality of samples as the fluid passes through said flow cytometer.

Such recitation does not appear to exclude incorporating a separate flow cytometer module as recited by Weigl, upon which the plurality of samples from the fluid flow stream as in the flow system of Saros, can be individually and separately introduced into the flow cytometer of Weigl for detection in the absence of separation gas. As recited, the claims read on a flow cytometer for hydrodynamic focusing that is a separate detection system from the single flow system of Saros comprising a means for moving samples and a means for introducing separation gas between samples. Accordingly, the teaching against separation gases in flow cytometry does not have relevancy in this rejection to the claimed invention since as recited, claim 1 does not exclude that the separation gases are not further introduced into the (separate) flow cytometer for hydrodynamic focusing and selective analysis of the particles in the samples.

To reiterate, Saros discloses a flow system comprising an autosampler for moving a plurality of samples, a means for introducing a separation gas between each sample, and the tubing for passage of fluid stream therethrough. The walls of the tubing have an expanded diameter sufficient to render the separation gas, non-occluding.

Weigl is combined therewith, for the disclosure of a (separate) flow module for performing analytical measurement and wherein particles are reproducibly focused in a measurement zone of the flow cytometer, and wherein selective analysis of particles in a plurality of samples takes place.

Allowable Subject Matter

10. Claim 52 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims, and if rewritten or amended to overcome the rejection under 35 U.S.C. 112, second paragraph, set forth in this Office action. In the specification, Applicant specifically provides that specific peristaltic flow rates (of at least about 3 ul /second) through common tubing of a given size (0.02 inch tubing, 10 rpm or higher) for introducing separation gas aliquots of a controlled volume (0.1 to at least about 10 ul), have been determined to be compatible with flow cytometric detection. These essential elements are critical to the practice of the invention.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 5:30 AM to 2:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gailene R. Gabel
Patent Examiner
Art Unit 1641
June 24, 2004

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
06/28/04